PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 487/04, 471/04, 491/14, A61K 31/40 // (C07D 487/04, 209:00, 209:00) (C07D 487/04, 223:00, 209:00) (C07D 471/04, 221:00, 209:00)

A1

(11) International Publication Number: **WO 00/12510**

(43) International Publication Date: 9 March 2000 (09.03.00)

(21) International Application Number: PCT/GB99/02884

(22) International Filing Date: 1 September 1999 (01.09.99)

(30) Priority Data:
9819035.8 1 September 1998 (01.09.98) GB

(71) Applicant *(for all designated States except US)*: CEREBRUS PHARMACEUTICALS LIMITED [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB).

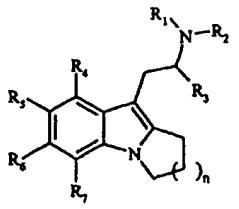
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ADAMS, David, Reginald [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). BENTLEY, Jonathan, Mark [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). ROFFEY, Jonathan, Richard, Anthony [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). HAMLYN, Richard, John [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). GAUR, Suneel [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). DUNCTON, Matthew, Alexander, James [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). DAVIDSON, James, Edward, Paul [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). BICKERDIKE, Michael, John [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). CLIFFE, Ian, Anthony [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). MANSELL, Howard, Langham [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB).

(74) Agent: HOWARD, Paul, Nicholas; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PYRROLOINDOLES, PYRIDOINDOLES AND AZEPINOINDOLES AS 5-HT2C AGONISTS



(I)

(57) Abstract

A chemical compound of formula (I), wherein n is 1, 2 or 3; R_1 and R_2 are independently selected from hydrogen and alkyl; R_3 is alkyl; R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, or R_5 and R_6 together form a carbocyclic or heterocyclic ring, and pharmaceutically acceptable salts and prodrugs thereof, and the use thereof in therapy, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders, diabetes insipidus, and sleep apnea, and particularly for the treatment of obesity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PYRROLOINDOLES, PYRIDOINDOLES AND AZEPINOINDOLES AS 5-HT2C AGONISTS

The present invention relates to pyrroloindole, pyridoindole and azepinoindole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

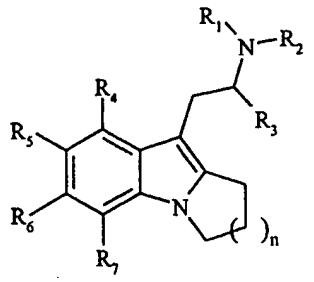
The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **96**, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **133**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. 2-(2,3-Dihydro-1*H*-pyrrolo[1,2-a]indol-9-yl)ethylamine is disclosed in *J.Med.Chem.*, 1965, **8**, 700. The preparation of pyrido[1,2-*a*]indoles for the treatment of cerebrovascular disorders is disclosed in EP-A-0252643 and EP-A-

0167901. The preparation of 10-[(acylamino)ethyl]tetrahydropyrido[1,2-*a*]indoles as anti-ischemic agents is disclosed in EP-A-0279125.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for $5\text{-}HT_{2B}$ and/or $5\text{-}HT_{2C}$ receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting $5\text{-}HT_{2C}$ receptor ligands, preferably $5\text{-}HT_{2C}$ receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

n is 1, 2 or 3;

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, or R_5 and R_6 together form a carbocyclic or heterocyclic ring,

and pharmaceutically acceptable salts and prodrugs thereof.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteratom, such as pyridyl, pyrrolyl, furanyl and thienyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

- alkyl,
- aryl,
- arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as

- haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),
- aldehydes (e.g. carboxaldehyde),
- ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),

acids (e.g. carboxy, carboxyalkyl),
acid derivatives such as esters
(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl),
carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy)
and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen-containing groups such as
amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),
azides,
nitriles (e.g. cyano, cyanoalkyl),
nitro;

sulfur-containing groups such as
thiols, thioethers, sulfoxides and sulfones
(e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom,
(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl,

pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical.

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

In a preferred embodiment, the compounds of formula (I) are selected from compounds in which n is 1.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen. In an embodiment of the invention, R_1 is hydrogen and R_2 is alkyl (preferably lower alkyl and more preferably methyl) optionally substituted by an aryl (preferably a substituted or unsubstituted phenyl or thienyl group) or by a cycloalkyl group (preferably saturated and preferably selected from a C_3, C_4, C_5, C_6 and C_7 cycloalkyl group).

Preferably, the compounds of formula (I) are selected from compounds in which R_3 is lower alkyl, preferably methyl or ethyl, preferably methyl. The carbon atom to which R_3 is bound is an asymmetric carbon atom. It is preferred that this asymmetric carbon atom is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R_3 is an unsubstituted alkyl group.

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, or R_5 and R_6 together form a carbocyclic or heterocyclic ring.

In an embodiment of the invention, R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl.

It is preferred that R_4 is selected from hydrogen and halogen, preferably hydrogen.

It is preferred that R_5 is selected from a substituent group other than hydrogen, and preferably from halogen, alkyl, alkoxy, alkylthio, alkylsulfonyl, monoalkylamino and dialkylamino, and more preferably from halogen (preferably fluoro, chloro and bromo), alkyl (preferably lower alkyl and preferably trifluoromethyl), alkoxy (preferably lower alkoxy) and alkylthio (preferably lower alkylthio).

It is preferred that R_6 is selected from halogen (preferably fluoro and chloro) and hydrogen. In an embodiment of the invention, R_6 is a substituent group other than hydrogen.

It is preferred that R_7 is hydrogen.

In an embodiment of the invention, two or three of R_4, R_5, R_6 and R_7, preferably two or three of R_4, R_6 and R_7, and preferably at least R_4 and R_7, are hydrogen.

In an embodiment of the invention, R_5 and R_6 may together form a carbocyclic or heterocyclic ring, preferably a heterocyclic ring. The ring may be a 4, 5, 6 or 7-membered ring, preferably a 5- or 6-membered ring, and preferably a 5-membered ring. The ring may be aliphatic or aromatic, preferably aliphatic. Where heterocyclic, the ring may contain 1, 2 or 3 heteroatoms, preferably 1 or 2 heteroatoms. The heteroatoms may be selected from O, S or N. The ring may be substituted or unsubstituted as defined above for "alkyl" groups and "aryl" groups. In a preferred embodiment, R_5 and R_6 together form a methylenedioxy group which forms a ring with the adjacent carbon atoms of the phenyl group to which it is bound. As used herein, the term "carbocyclic ring" means a ring in which each of the ring atoms are carbon atoms.

In a preferred embodiment, the compounds of formula (I) are selected from 1-(7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(6,7-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(7-bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and 1-(7-methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, and particularly the (*S*)-enantiomers thereof. Where the compounds of formula (I) are in salt form, the fumarate salts are preferred.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the term "substantially free of its (*R*)-enantiomer" means that a composition comprising a compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

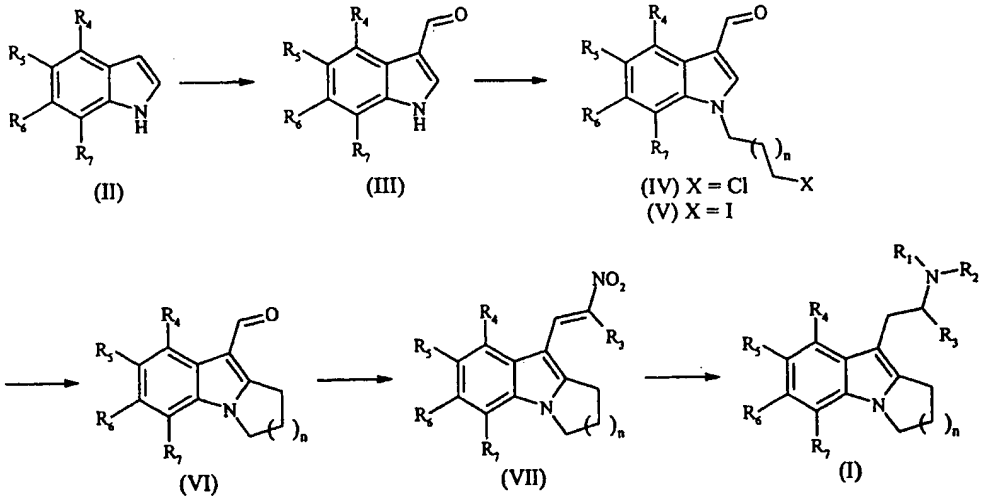
According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I).

Compounds of the invention may be prepared according to Reaction Scheme 1 below. R_1 to R_7 are as previously defined. The aldehyde (III) may be prepared by reaction of indole (II) with for example, phosphorus oxychloride in dimethylformamide. The chloride (IV) can be formed from the aldehyde (III) by reaction with a suitable bromo-chloro-alkane, iodo-chloro-alkane or chloro-alkane-sulfonate in the presence of a base such as potassium hydroxide in a solvent such as dimethyl sulfoxide. Formation of the iodide (V) may be achieved by reaction of the chloride (IV) with an iodide salt such as sodium iodide in a solvent such as acetonitrile. The aldehyde (VI) may be formed by reaction of the iodide (V) with a trialkyltin hydride in the presence of a reagent such as 1,1'-azobis(cyclohexanecarbonitrile) or azobisisobutyronitrile in a solvent such as toluene. The nitroalkene (VII) may be obtained by reaction of the aldehyde (VI) with a nitroalkane. Compounds of formula (I) can be formed in the reaction of the nitroalkene (VII) with a reducing agent such as lithium aluminium hydride in an ethereal solvent.

Reaction Scheme 1



The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) (R_1 = R_2 = H) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

If, in any of the processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives

such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from

gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, 9, 3482-90.

The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	K_i (2C) nM	K_i (2B) nM	K_i (2A) nM
Example 1	110	229	457
Example 2	97	102	257
Example 3	118	220	151
Example 5	81	122	448
Example 11	84	115	316

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of compounds of formula (I) is shown in Table 2.

Table 2

Compound	h5-HT_{2A}		h5-HT_{2C}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example 1	3236	33	96	68
Example 2	>1000	12	147	38
Example 3	636	22	32	63
Example 5	4020	33	94	69
Example 6	>10000	-	348	56
Example 7	2620	37	227	59
Example 8	921	36	33	58
Example 9	792	40	7	81
Example 11	>10000	-	8	80

3. *In Vivo* Efficacy

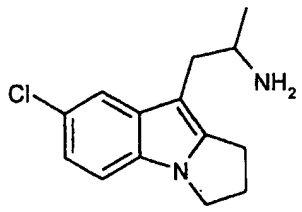
The *in vivo* efficacy of 5-HT_{2C} agonists was assessed by the ability of the compounds to induce three specific behaviours ($5HT_{2C}$ Syndrome) in rats.

The 5-HT_{2c} syndrome is a rapid screening method to assess the *in vivo* efficacy of 5-HT_{2c} agonists through their ability to induce three specific behaviours in rats. The animals were dosed with either a positive control (mCPP), test compound or vehicle, either sub-cutaneously or p.o.. The animals were observed on an open bench, typically 30, 60 and 180 minutes after dosing and the degree of syndrome was assessed over a two minute period on a scale of 0-3 depending on the presence and severity of splayed limbs, hunched posture and retro-pulsion, the three specific behaviours which constitute the syndrome. Data were analysed using Kruskal-Wallis Analysis of Variance followed with appropriate post-hoc tests. All statistical analysis were conducted using Excel version 7.0 (Microsoft Corp.) and Statistica version 5.0 (Statsoft, Inc.).

The thus determined activity of Example 3 indicates that after a dose of 20 mg/kg s.c. the compound maintains significant pharmacological efficacy for at least 180 minutes.

Synthetic Examples

Example 1: (*RS*)-1-(7-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hydrochloride



5-Chloroindole-3-carboxaldehyde

To stirred dimethylformamide (20 mL) at 0 °C was added dropwise phosphorus oxychloride (4.6 mL, 49 mmol). The mixture was stirred for 10 min and a solution of 5-chloroindole (5.0 g, 33 mmol) in dimethylformamide (5 mL) was added dropwise. The mixture was heated to 40 °C for 45 min, cooled to room temperature and then treated with a solution of sodium hydroxide (5.9 g, 148 mmol) in water (20 mL). The mixture was heated to 50 °C for 10 min, cooled to room temperature, poured onto crushed ice (100 mL) and filtered. The filter cake was recrystallised (methanol) to give the product as a white solid (3.5 g, 59%): mp 215-216 °C; Found: C, 60.13; H, 3.40; N, 7.75%. C_9H_6ClNO requires: C, 60.19; H, 3.37; N, 7.79%.

5-Chloro-1-(3-chloropropyl)indole-3-carboxaldehyde

To a stirred mixture of powdered potassium hydroxide (85%, 2.6 g, 39 mmol) in methyl sulfoxide (20 mL) was added dropwise a solution of 5-chloroindole-3-carboxaldehyde (3.5 g, 19 mmol) in methyl sulfoxide (5 mL). The mixture was stirred for 30 min and 1-bromo-3-chloropropane (2.9 mL, 29 mmol) was added dropwise. The mixture was stirred for 1 h and partitioned between ethyl acetate (3 x 40 mL) and water (100 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo*. The solid residue was recrystallised (2-propanol) to give the product as a white solid (4.1 g, 82%): mp 107-108 °C; Found: C, 56.51; H, 4.26; N, 5.44%. $C_{12}H_{11}Cl_2NO$ requires: C, 56.27; H, 4.33; N, 5.47%.

5-Chloro-1-(3-iodopropyl)indole-3-carboxaldehyde

A stirred solution of 5-chloro-1-(3-chloropropyl)indole-3-carboxaldehyde (3.8 g, 15 mmol) and sodium iodide (4.5 g, 30 mmol) in acetonitrile (50 mL) under argon was heated under reflux for 18 h, cooled to room temperature and partitioned between ether (3 x 30 mL) and water (50 mL). The combined organic extracts were washed (aqueous sodium metabisulfite solution, water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product as a yellow oil (5.0 g, 96%) which was used immediately.

7-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

To a stirred solution of 5-chloro-1-(3-iodopropyl)indole-3-carboxaldehyde (5.0 g, 14 mmol) in toluene (75 mL) at reflux under argon was added dropwise over 2 h a solution of 1,1'-azobis(cyclohexanecarbonitrile) (3.5 g, 14 mmol) and tri-n-butyltin hydride (7.8 mL, 29 mmol) in toluene (75 mL). The mixture was stirred for 3 h, cooled to room temperature, and potassium fluoride (3.5 g, 60 mmol) and water (15 mL) were added. The mixture was stirred for 18 h and filtered through a pad of kieselguhr. The filter-cake was washed (ethyl acetate) and the filtrate was concentrated *in vacuo*, purified by column chromatography [SiO_2; ethyl acetate-hexane (9:1)] and recrystallised (methanol) to give the product as a white solid (1.1 g, 36%): mp 179-180 °C; Found: C, 65.54; H, 4.61; N, 6.38%. $C_{12}H_{10}ClNO$ requires: C, 65.61; H, 4.59; N, 6.37%.

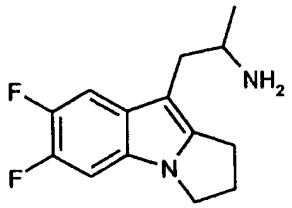
1-(7-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

A stirred solution of 7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (1.0 g, 4.6 mmol) and ammonium acetate (0.4 g, 5.2 mmol) in nitroethane (10 mL) was heated to 100 °C for 1 h, cooled to room temperature, diluted with methanol (30 mL), cooled to 0 °C, and filtered. The filter-cake was recrystallised (toluene) to give the product as yellow needles (0.58 g, 46%): mp 162-1623 °C; Found: C, 60.68; H, 4.67; N, 9.98%. $C_{14}H_{13}ClN_2O_2$ requires: C, 60.77; H, 4.73; N, 10.12%.

(*RS*)-1-(7-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hydrochloride

To a stirred solution of lithium aluminium hydride (1.0 M in THF, 2.7 mL, 2.7 mmol) in added THF (5 mL) under argon was added dropwise a solution of 1-(7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene (0.5 g, 1.8 mmol) in THF (10 mL). The mixture was heated under reflux for 4 h and cooled to 0 °C. To the mixture was added dropwise aqueous potassium sodium tartrate solution (50 mL) and the mixture was stirred for 30 min and filtered through kieselguhr. The filtrate was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate), concentrated *in vacuo*, treated with ethereal hydrogen chloride (1.0 M, 2 mL, 2 mmol) and concentrated *in vacuo*. The concentrate was recrystallised (2-propanol) to give the title compound as a white solid (0.23 g, 45%): mp 272-273 °C; Found: C, 57.86; H, 6.37; N, 9.41%. $C_{14}H_{17}ClN_2.HCl.0.25H_2O$ requires: C, 58.03; H, 6.39; N, 9.67%.

Example 2: (*RS*)-1-(6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hydrochloride



5,6-Difluoroindole-3-carboxaldehyde

5,6-Difluoroindole-3-carboxaldehyde was prepared from 5,6-difluoroindole according to the method described in Example 1 to give 2.9 g (78%) of the product as a pale yellow solid: mp 236-238 °C; Found: C, 58.34; H, 2.79; N, 7.27%. $C_9H_5F_2NO.0.25H_2O$ requires: C, 58.23; H, 2.99; N, 7.55%.

5,6-Difluoro -1-(3-chloropropyl)indole-3-carboxaldehyde

5,6-Difluoro -1-(3-chloropropyl)indole-3-carboxaldehyde was prepared from 5,6-difluoroindole-3-carboxaldehyde according to the method described in Example 1 to give the 2.9 g (78%) of the product as a yellow solid: mp 111-113 °C; Found: C, 55.87; H, 3.94; N, 5.40%. $C_{12}H_{10}ClF_2NO$ requires: C, 55.94; H, 3.91; N, 5.44%.

5,6-Difluoro-1-(3-iodopropyl)indole-3-carboxaldehyde

5,6-Difluoro-1-(3-iodopropyl)indole-3-carboxaldehyde was prepared from 5,6-difluoro -1-(3-chloropropyl)indole-3-carboxaldehyde according to the method described in Example 1 with the following modification: the crude product was purified by column chromatography [SiO_2; hexane-ethyl acetate (3:2)] to give the product as a yellow solid (2.7 g, 87%). A sample recrystallised from ethyl acetate-hexane gave mp 95-97 °C; Found: C, 41.42; H, 2.94; N, 3.99%. $C_{12}H_{10}F_2INO$ requires: C, 41.28; H, 2.89; N, 4.01%.

6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 5,6-difluoro-1-(3-iodopropyl)indole-3-carboxaldehyde according to the method described in Example 1 with the following modification: the crude product was purified by column chromatography [SiO_2; hexane-ethyl acetate (1:1)] to give the product as a pale yellow solid (1.1 g, 66%) which was used immediately without further purification.

1-(6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

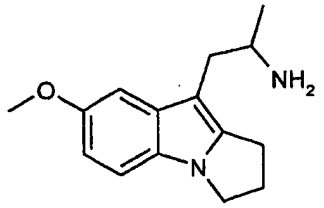
1-(6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 6,7-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 with the following modifications: the reaction mixture was stirred at 100 °C for 1 h, cooled to room temperature and partitioned between ethyl acetate (3 x 30 mL) and water. The combined organic

extracts were washed (brine), dried (magnesium sulfate) and concentrated *in vacuo* to give the crude product which was purified by column chromatography [SiO_2; hexane-ethyl acetate (3:1)] to give the product as a yellow solid (0.9 g, 72%). A sample recrystallised from methanol gave mp 156-8 °C; Found: C, 62.63; H, 5.42; N, 9.30%. $C_{14}H_{12}F_2N_2O_2.0.3C_6H_{14}$ requires: C, 62.40; H, 5.37; N, 9.21%.

(*RS*)-1-(6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hydrochloride

(*RS*)-1-(6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hydrochloride was prepared from 1-(6,7-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 1 with the following modifications: the reaction mixture was heated under reflux for 4 h, cooled to 0 °C and poured into aqueous potassium sodium tartrate solution (150 mL) and diethyl ether (100 mL). The mixture was stirred for 30 min, filtered through celite® and the filtrate was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed (brine), dried (magnesium sulfate), concentrated *in vacuo*, treated with ethereal hydrogen chloride (1.0 M, 2 mL, 2 mmol) and concentrated *in vacuo*. The residue was recrystallised (ethyl acetate, 2-propanol) to give the title compound as a white solid (0.55 g, 63%): mp 264-266 °C. Found: C, 58.67; H, 6.09; N, 9.65%. $C_{14}H_{16}F_2N_2.HCl$ requires: C, 58.64; H, 5.98; N, 9.76%.

Example 3: (*RS*)-1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



5-Methoxyindole-3-carboxaldehyde

5-Methoxyindole-3-carboxaldehyde was prepared from 5-methoxyindole according to the method described in Example 1 to give 5.1 g (85%) of the product as a white solid: mp 179-180 °C; Found: C, 68.37; H, 5.15; N, 7.98%. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 7.99%.

1-(3-Chloropropyl)-5-methoxy-indole-3-carboxaldehyde

1-(3-Chloropropyl)-5-methoxy-3-carboxaldehyde was prepared from 5-methoxyindole-3-carboxaldehyde according to the method described in Example 1 with the following modifications: the reaction mixture was stirred for 18 h, poured into ice-water (100 mL) and filtered. The filter-cake was recrystallised [isopropyl ether, 2-propanol (1:1)] to give the product as a white, crystalline solid (4.6 g, 63%): mp 75-76 °C; NMR δ_H (400 MHz, $CDCl_3$) 2.29 (2H, quintet, *J* 6 Hz) 3.46 (2H, t, *J* 6 Hz) 3.87 (3H, s) 4.36 (2H, t, *J* 6 Hz) 6.95 (1H, dd, *J* 2.5, 9 Hz) 7.27 (1H, d, *J* 9 Hz) 7.69 (1H, s) 7.77 (1H, d, *J* 2.5 Hz) 9.94 (1H, s).

1-(3-Iodopropyl)-5-methoxy-indole-3-carboxaldehyde

1-(3-Iodopropyl)-5-methoxy-indole-3-carboxaldehyde was prepared from 1-(3-chloropropyl)-5-methoxy-indole-3-carboxaldehyde according to the method described in Example 1 with the following modification: the reaction mixture was heated under reflux for 18 h, cooled to room temperature and partitioned between ether (3 x 30 mL) and water (50 mL). The combined organic extracts were washed (aqueous sodium metabisulfite solution, water, brine), dried (sodium sulfate) and concentrated *in vacuo*. The crude product was purified by column chromatography [SiO_2; heptane-ethyl acetate (3:1)] to give the product as a yellow oil (4.9 g, 78%) which was used immediately.

7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 1-(3-iodopropyl)-5-methoxy-indole-3-carboxaldehyde according to the method described in Example 1 to give 0.41 g (13%) of the product as a white solid: mp 151-

152 °C; Found: C, 72.25; H, 6.10; N, 6.46%. $C_{13}H_{13}NO_2$ requires: C, 72.54; H, 6.09; N, 6.50%.

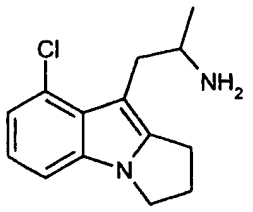
1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 with the following modification: the reaction mixture was heated to 100 °C for 1 h, cooled to room temperature and partitioned between ethyl acetate (2 x 20 mL) and water (30 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-heptane (1:1)] to give the product as yellow needles (0.46 g, 91%): mp 143 °C; Found: C, 66.32; H, 5.89; N, 10.27 %. $C_{15}H_{16}N_2O_3$ requires: C, 66.16; H, 5.92; N, 10.28%.

(*RS*)-1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

(*RS*)-1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from 1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 1 with the following modifications: the reaction mixture was heated under reflux for 4 h, cooled to 0 °C and aqueous potassium sodium tartrate solution (50 mL) was added slowly. The mixture was stirred for 30 min, filtered through a pad of kieselguhr and the filtrate was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo*. The concentrate was dissolved in 2-propanol (1 mL) and added to a solution of fumaric acid (0.17 g, 1.5 mmol) in 2-propanol (20 mL) at 50 °C. The solution was cooled to 0 °C and filtered. The filter-cake was washed (2-propanol, ether) and dried to give the title compound as a white solid (0.22 g, 42%): mp 194-196 °C; Found: C, 63.27; H, 6.80; N, 7.69%. $C_{19}H_{24}N_2O_5$ requires: C, 63.32; H, 6.71; N, 7.77%.

Example 4: (*RS*)-1-(8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hemifumarate



4-Chloroindole-3-carboxaldehyde

4-Chloroindole-3-carboxaldehyde was prepared from 4-chloroindole according to the method described in Example 1 to give 7.8 g (100%) of the product which was used without further purification.

4-Chloro-1-(3-chloropropyl)indole-3-carboxaldehyde

4-Chloro-1-(3-chloropropyl)indole-3-carboxaldehyde was prepared from 4-chloroindole-3-carboxaldehyde according to the method described in Example 1 to give 3.8 g (45%, from 4-chloroindole) of the product as a white solid: mp 89 °C; Found: C, 56.16; H, 4.23; N, 5.40%. $C_{12}H_{11}Cl_2NO$ requires: C, 56.27; H, 4.33; N, 5.47%.

4-Chloro-1-(3-iodopropyl)indole-3-carboxaldehyde

4-Chloro-1-(3-iodopropyl)indole-3-carboxaldehyde was prepared from 4-chloro-1-(3-chloropropyl)indole-3-carboxaldehyde according to the method described in Example 1 to give 4.2 g (83%) of the product as a yellow solid which was used immediately without further purification.

8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 4-chloro-1-(3-iodopropyl)indole-3-carboxaldehyde according to the method described in

Example 1 to give 1.0 g (39%) of the product as a white solid; mp 160-161 °C; Found: C, 65.70; H, 4.54; N, 6.34%. $C_{12}H_{10}NClO$ requires: C, 65.61; H, 4.59; N, 6.37%.

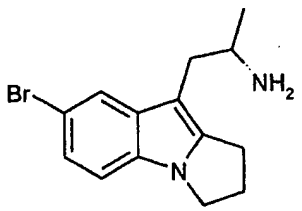
1-(8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-(8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 8-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 3 to give 1.1 g (95%) of the product as yellow needles: mp 137-138 °C; Found: C, 60.68; H, 4.73; N, 9.95%. $C_{14}H_{13}N_2ClO_2$ requires: C, 60.77; H, 4.73; N, 10.12%.

(*RS*)-1-(8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hemifumarate

(*RS*)-1-(8-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine hemifumarate was prepared from 1-(8-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.71 g (53%) of the product as a white solid. A sample recrystallised from 2-propanol gave mp 207-208 °C; Found: C, 61.67; H, 6.31; N, 8.79%. $C_{14}H_{17}N_2Cl.0.5C_4H_4O_4.0.25H_2O$ requires: C, 61.73; H, 6.31; N, 9.00%.

Example 5: (*RS*)-1-(7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



5-Bromoindole-3-carboxaldehyde

5-Bromoindole-3-carboxaldehyde was prepared from 5-bromoindole according to the method described in Example 1 to give 5.1 g (89%) of the product as a beige solid which was used without further purification: IR ν_{max} (Nujol)/cm^{-1} 3222, 2925, 2855, 1712, 1644, 1524, 1459, 1441, 1378, 1290, 1129, 1096, 856, 799, 782, 728, 673, 609 and 573; NMR δ_H (400 MHz, $CDCl_3$) 6.31 (1H, dd, *J* 2, 8.5 Hz) 6.41 (1H, d, *J* 8.5 Hz) 7.13 (1H, d, *J* 2 Hz) 7.26 (1H, s) 8.84 (1H, s) 11.21 (1H, s).

5-Bromo-1-(3-chloropropyl)indole-3-carboxaldehyde

5-Bromo-1-(3-chloropropyl)indole-3-carboxaldehyde was prepared from 5-bromoindole-3-carboxaldehyde according to the method described in Example 1 with the following modification: the reaction mixture was stirred for 18 h, poured into ice-water (200 mL) and filtered. The filter-cake was washed (water, heptane), dried and purified by column chromatography (SiO_2; ethyl acetate) to give 4.6 g (77%) of the product as a white solid: IR ν_{max} (Nujol)/cm^{-1} 2925, 2855, 1660, 1610, 1532, 1469, 1402, 1378, 1302, 1171, 1195, 1035, 968, 818, 786, 722, 666, 622 and 610; NMR δ_H (400 MHz, $CDCl_3$) 2.32 (2H, m) 3.48 (2H, t, *J* 6.5 Hz) 4.41 (2H, t, *J* 6.5 Hz) 7.28 (1H, d, *J* 9 Hz) 7.44 (1H, dd, *J* 2, 8.5 Hz) 7.76 (1H, s) 8.47 (1H, d, *J* 3 Hz) 9.98 (1H, s).

5-Bromo-1-(3-iodopropyl)indole-3-carboxaldehyde

5-Bromo-1-(3-iodopropyl)indole-3-carboxaldehyde was prepared from 5-chloro-1-(3-chloropropyl)indole-3-carboxaldehyde according to the method described in Example 1 to give 6.0 g (100%) of the product as a yellow oil which was immediately.

7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 5-bromo-1-(3-iodopropyl)indole-3-carboxaldehyde according to the method described in Example 1 to give 1.2 g (32%) of the product as a white solid: mp 189-191 °C; IR ν_{max} (Nujol)/cm^{-1} 2925, 2855, 1651, 1606, 1534, 1452, 1442, 1397, 1377, 1360, 1314, 1288, 1245, 1050, 1038, 802, 775, and 571; NMR δ_H (400 MHz, $CDCl_3$) 2.72 (2H, m)

3.25 (2H, t, *J* 7.5 Hz) 4.08 (2H, t, *J* 7 Hz) 7.07 (1H, d, *J* 8.5 Hz) 7.29 (1H, d, *J* 8.5 Hz) 8.31 (1H, s) 9.90 (1H, s).

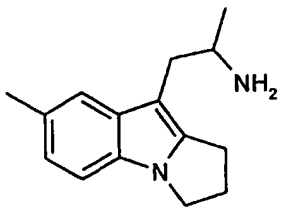
1-(7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-(7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 7-bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 to give 1.1 g (81%) of the product as yellow needles: mp 173 °C; Found: C, 52.44; H, 4.10; N, 8.75 %. $C_{14}H_{13}N_2BrO$ requires: C, 52.36; H, 4.08; N, 8.72%.

(*RS*)-1-(7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

(*RS*)-1-(7-Bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from 1-(7-bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.38 g (60%) of the product as a white solid: mp 181-183 °C; IR ν_{max} (Nujol)/cm^{-1} 2925, 2855, 1702, 1632, 1580, 1524, 1464, 1378, 1317, 1277, 1222, 1167, 1100, 1049, 986, 897, 783 722, 652 and 564; NMR δ_H (400 MHz, DMSO- d_6) 1.14 (3H, d, *J* 7 Hz) 2.56 (2H, m) 2.96 (3H, m) 3.79 (1H, m) 4.05 (2H, t, *J* 7 Hz) 6.46 (2H, s) 7.15 (1H, dd, *J* 2, 8.5 Hz) 7.27 (1H, d, *J* 8.5 Hz) 7.72 (1H, d, *J* 2 Hz).

Example 6: (*RS*)-1-(7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



5-Methylindole-3-carboxaldehyde

5-Methylindole-3-carboxaldehyde was prepared from 5-methylindole according to the method described in Example 1 to give 2.06 (42%) of the product as a pink solid: mp 148-149 °C; IR ν_{max} (Nujol)/cm^{-1} 3145, 2924, 1639, 1523, 1450, 1133, 805 and 616; NMR δ_H (400 MHz, DMSO-d_6) 2.41 (3H, s), 3.32 (3H, s), 7.08 (1H, d, *J* 6.7 Hz), 7.39 (1H, d, *J* 8.2 Hz), 7.90 (1H, s), 8.22 (1H, s), 9.90 (1H, s) and 12.01 (1H, br. s); Found: C, 75.24; H, 5.67; N, 8.83%. $C_{10}H_9NO$ requires: C, 75.45; H, 5.70; N, 8.97%.

1-(3-Chloropropyl)-5-methyl-indole-3-carboxaldehyde

1-(3-Chloropropyl)-5-methyl-indole-3-carboxaldehyde was prepared from 5-methylindole-3-carboxaldehyde according to the method described in Example 1 to give 2.26 g (76%) of the product as an off-white solid: mp 89-90 °C; IR ν_{max} (Nujol)/cm^{-1} 2956, 1659, 1536, 1403, 1171, 820 and 786; NMR δ_H (400 MHz, $CDCl_3$) 2.27-2.34 (2H, m), 2.47 (3H, s), 3.46 (2H, t, *J* 6.2 Hz), 4.38 (2H, t, *J* 6.6 Hz), 7.16 (1H, d, *J* 10 Hz), 7.28 (1H, d, *J* 8.4 Hz), 7.70 (1H, s), 8.12 (1H, s) and 9.97 (1H, s); Found: C, 66.12; H, 6.00; N, 5.88%. $C_{13}H_{14}ClNO$ requires: C, 66.24; H, 5.99; N, 5.94%.

1-(3-Iodopropyl)-5-methyl-indole-3-carboxaldehyde

1-(3-Iodopropyl)-5-methyl-indole-3-carboxaldehyde was prepared from 1-(3-chloropropyl)-5-methyl-indole-3-carboxaldehyde according to the method described in Example 1 to give the product as pink oil which was used immediately without further purification.

7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 1-(3-iodopropyl)-5-methyl-indole-3-carboxaldehyde according to the method described in Example 1 to give 0.74 g (40%) of the product as a white solid: mp 148-149 °C; IR ν_{max} (Nujol)/cm^{-1} 2953, 1643, 1448, 1357, 1033 and 814; NMR δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s), 2.68-2.73 (2H, m), 3.27 (2H, t, *J* 7.7 Hz), 4.09 (2H, t, *J* 7.5 Hz), 7.04 (1H, d, *J* 8.5 Hz), 7.13 (1H, d, *J* 8.6 Hz), 8.00 (1H, s) and 9.96 (1H, s)

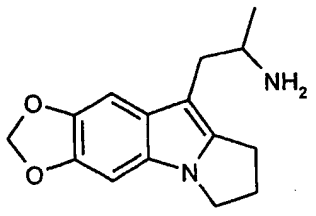
1-(7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-(7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 to give 0.73 g (68%) of the product as an orange solid: mp 138-139 °C; IR ν_{max} (Nujol)/cm^{-1} 2925, 1634, 1458, 1266, 1042, 977 and 799; NMR δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s), 2.46 (3H, s), 2.65-2.70 (2H, s), 3.10 (2H, t, *J* 7.0 Hz), 4.13 (2H, t, *J* 7.0 Hz), 7.04 (1H, d, *J* 7.0 Hz), 7.15 (1H, d, *J* 8.0 Hz), 7.41 (1H, s) and 8.39 (1H, s); Found: C, 70.57; H, 6.76; N, 11.14%. $C_{15}H_{16}N_2O_2$ requires: C, 70.29; H, 6.29; N, 10.92%.

(*RS*)-1-(7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

(*RS*)-1-(7-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from 1-(7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.61 g (71%) of the title compound as an off-white solid: mp darkens at 140 °C, melts 156-157 °C; IR ν_{max} (Nujol)/cm^{-1} 2922, 1697, 1461, 1378, 979, 791 and 652; NMR δ_H (400 MHz, DMSO-d_6) 1.25 (3H, d, *J* 6.5 Hz), 2.47 (3H, s), 2.63-2.67 (1H, m), 2.80-2.85 (1H, m), 2.94-3.08 (3H, m), 3.43-3.53 (2H, m), 4.10 (2H, t, *J* 7.4 Hz), 6.52 (2H, s), 6.97 (1H, d, *J* 8.1 Hz), 7.26 (1H, d, *J* 7.9 Hz) and 7.36 (1H, s); Found: C, 64.71; H, 7.30; N, 8.12%. $C_{15}H_{20}N_2.C_4H_4O_4.0.5H_2O$ requires: C, 64.57; H, 7.13; N, 7.93%.

Example 7: (*RS*)-1-[6,7-(Methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl]-2-propylamine fumarate



5,6-(Methylenedioxy)indole-3-carboxaldehyde

5,6-(Methylenedioxy)indole-3-carboxaldehyde was prepared from 5,6-(methylenedioxy)indole according to the method described in Example 1 to give 1.9 g (85%) of the product as a yellow solid: mp darkens and decomposes over 180-190 °C; IR ν_{max} (nujol)/cm^{-1} 3233, 2925, 1630, 1472, 1294, 1177 and 937; NMR δ_H (400 MHz, DMSO-d_6) 6.01 (2H, s), 7.03 (1H, s), 7.46 (1H, s), 8.08 (1H, s), 9.83 (1H, s) and 12.90 (1H, br. s).

1-(3-Chloropropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde

1-(3-Chloropropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde was prepared from 5,6-(methylenedioxy)indole-3-carboxyaldehyde according to the method described in Example 1 to give 2.06 g (79%) of the product as light-brown crystals: mp 108-109 °C; IR ν_{max} (nujol)/cm^{-1} 2924, 1656, 1534, 1250, 1163 and 939; NMR δ_H (400 MHz, $CDCl_3$) 2.27-2.30 (2H, m), 3.47 (2H, t, *J* 6 Hz), 4.30 (2H, t, *J* 6 Hz), 5.98 (2H, s), 6.82 (1H, s), 7.59 (1H, s), 7.70 (1H, s) and 9.90 (1H, s); Found: C, 58.92; H, 4.60; N, 5.23 %. $C_{13}H_{12}ClNO_3$ requires: C, 58.77; H, 4.55; N, 5.27 %.

1-(3-Iodopropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde

1-(3-Iodopropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde was prepared from 1-(3-chloropropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde according to the method described in Example 1 to give the product as a brown solid which was used immediately without further purification.

6,7-(Methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

This was prepared from 1-(3-iodopropyl)-5,6-(methylenedioxy)-indole-3-carboxaldehyde according to the method described in Example 1 to give 1.0 g (75 %) of the product as an off-white solid: mp 169-170 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1639, 1645, 1244, 1133 and 944; NMR δ_H (400 MHz, $CDCl_3$) 2.68 (2H, quint, *J* 7.2 Hz), 7.20

(2H, t, *J* 7.2 Hz), 4.05 (2H, t, *J* 7.1 Hz), 5.95 (2H, s), 6.70 (1H, s), 7.63 (1H, s) and 9.89 (1H, s).

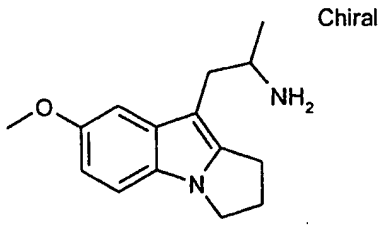
1-[6,7-(Methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-[6,7-(Methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 5,6-(methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 to give 0.76 g (62%) of the product as an orange solid: mp darkens over 202-210 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1635, 1458, 1246, 1197 and 861; NMR δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s), 2.65 (2H, quint, *J* 7.4 Hz), 3.06 (2H, t, *J* 7.6 Hz), 4.07 (2H, t, *J* 7.1 Hz), 5.95 (2H, s), 6.71 (1H, s), 7.00 (1H, s) and 8.30 (1H, s); Found: C, 62.31; H, 5.25; N, 9.93%. $C_{15}H_{14}N_2O_4$ requires: C, 62.93; H, 4.93; N, 9.78%.

(*RS*)-1-[(6,7-Methylenedioxy)-2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

(*RS*)-1-[(6,7-Methylenedioxy)-2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from 1-[6,7-(methylenedioxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.13 g (14%) of the title compound as an off-white solid: mp darkens over 135-140 °C; IR ν_{max} (Nujol)/cm^{-1} 2923, 1632, 1466, 1235, 1039 and 652; NMR δ_H (400 MHz, DMSO-d_6) 1.12 (3H, d, *J* 6.6 Hz), 2.46-2.53 (1H, m), 2.63-2.69 (1H, dd, *J*, 14.1, 8.4 Hz), 2.81-2.93 (3H, m), 3.26-3.39 (2H, m), 3.94 (2H, t, *J* 7.0 Hz), 5.89 (2H, s), 6.40 (2H, s), 6.89 (1H, s) and 7.01 (1H, s); Found: C, 58.48; H, 5.79; N, 7.25%. $C_{15}H_{18}N_2O_2.C_4H_4O_4.H_2O$ requires: C, 58.16; H, 6.16; N, 7.14%.

Examples 8 and 9: Enantiomer 1 and Enantiomer 2 of 1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



(*RS*)-1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-(trifluoroacetamido)-propane

To a stirred solution of (*RS*)-1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine (0.28 g, 1.1 mmol) in dichloromethane (10 mL) at 0 °C was added dropwise trifluoroacetic anhydride (0.18 mL, 1.3 mmol). The mixture was stirred for 1 h, concentrated *in vacuo* and purified by column chromatography (SiO_2; ether) to afford the product (0.39 g, 100%) as a beige solid: mp 131-3 °C; IR ν_{max} (Nujol)/cm^{-1} 3307, 3105, 2925, 2855, 2727, 1784, 1695, 1501, 1377, 1249, 1228, 1194, 1171, 1041, 844, 784 and 724; NMR δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5 Hz) 2.60 (2H, m) 2.92 (4H, m) 3.85 (3H, s) 4.03 (2H, t, *J* 7 Hz) 4.36 (1H, m) 6.37 (1H, d, *J* 6.5 Hz, NH) 6.79 (1H, dd, *J* 2.5, 8.5 Hz) 6.96 (1H, d, *J* 3 Hz) 7.11 (1H, d, *J* 9 Hz).

Enantiomer 1 and Enantiomer 2 of 1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-(trifluoroacetamido)-propane

(*RS*)-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-(trifluoroacetamido)-propane (0.10 g, 0.29 mmol) was dissolved in dichloromethane (500 μL) and half of the resultant solution was repeat-loaded onto a Chiralcel OD column (300mm × 4.6 mm) [10μL injections; 1.0 mL/min; hexane-2-propanol (90:10); 220 nm] to afford, after removal of solvent, enantiomer 1 of (7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-(trifluoroacetamido)-propane (0.018 g, 36%) as an off-white solid; LC: [Chiralcel OD; hexane-2-propanol (90:10); 1.0 mL/min; 220 nm] 99.1% (11.59 min) and 0.9% (15.90 min); [Supelcosil ABZ+; methanol-10mM aqueous ammonium acetate solution (80:20)] 96.4% (3.08 min); and (*S* or *R*)-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-

a]indol-9-yl)-2-(trifluoroacetamido)-propane (0.018 g, 36%, 92% e.e.) as a pale green solid; LC: [Chiralcel OD; hexane-2-propanol (90:10); 1.0 mL/min; 220 nm] 4.0% (11.47 min) and 96.0% (15.76 min); [Supelcosil ABZ+; methanol-10mM aqueous ammonium acetate solution (80:20)] 94% (3.09 min).

Enantiomer 1 of 1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-propylamine fumarate

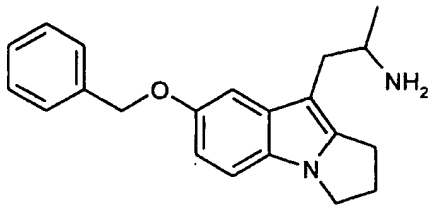
To a solution of the first-eluting trifluoroacetamide enantiomer (0.018 g, 0.05 mmol) in methanol (10 mL) was added potassium carbonate (0.02 g, 0.14 mmol) and 5 drops of water, and the resultant suspension was stirred for 18 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate, dried (magnesium sulfate), concentrated *in vacuo* and purified by flash column chromatography [SiO_2; ethyl acetate → ethyl acetate-methanol-0.880 ammonia solution (90:8:2)] to afford a colourless oil (0.0055 g). The oil was dissolved in 2-propanol (0.1 mL) and added to a solution of fumaric acid (0.0039 g, 0.034 mmol) in 2-propanol (1 mL) at 50 °C and the mixture was evaporated to a residual amount of solvent. Ether was added, and the mixture was filtered. The filter-cake was washed with cold ether to afford the product (0.0035 g, 43%) as a white solid: LC: [Supelcosil ABZ+; methanol-10mM aqueous ammonium acetate solution (70:30)] 94% (1.95 min); LC (sample treated with excess trifluoroacetic anhydride): [Chiralcel OD; hexane-2-propanol (90:10); 1.0 mL/min; 220 nm] > 99% (12.28 min); *m/z* (ES^+) 308 [$(M + Na + MeCN)^+$, 5%], 245 (MH^+, 7%) and 228 [$(MH - NH_3)^+$, 100%].

Enantiomer 2 of 1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

enantiomer 2 of 1-(7-Methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from second-eluting trifluoroacetamide enantiomer according to the method described above to give 0.0018 g (25%) of the product as a white solid: LC: [Supelcosil ABZ+; methanol-10mM aqueous ammonium acetate solution (80:20)] 98% (1.69 min); LC (sample treated with excess trifluoroacetic anhydride): [Chiralcel OD;

hexane-2-propanol (90:10); 1.0 mL/min; 220 nm] 1% (12.58 min) and 99% (17.07 min); *m/z* (ES^+) 245 (MH^+, 5 %) and 228 [$(MH - NH_3)^+$, 100%].

Example 10: (*RS*)-1-(7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



5-Benzyloxylindole-3-carboxaldehyde

5-Benzyloxylindole-3-carboxaldehyde was prepared from 5-benzyloxyindole according to the method described in Example 1 to give the crude product as a pale-brown solid which was used immediately without further purification.

5-Benzyloxy-1-(3-chloropropyl)indole-3-carboxaldehyde

5-Benzyloxy-1-(3-chloropropyl)indole-3-carboxaldehyde was prepared from 5-benzyloxylindole-3-carboxaldehyde according to the method described in Example 1 to give 4.4 g (68% from 5-benzyloxyindole) of the product as brown needles: mp 134-135 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1655, 1527, 1228, 1036, 787 and 707; NMR δ_H (400 MHz, $CDCl_3$) 2.28 (2H, m), 3.45-3.48 (2H, t, *J* 5.9 Hz), 4.37 (2H, t, *J* 6.5 Hz), 5.13 (2H, s), 7.05 (1H, dd, *J* 9.1, 2.5 Hz), 7.28-7.48 (6H, m), 7.70 (1H, s), 7.91 (1H, d, *J*, 2.5 Hz) and 9.96 (1H, s); Found: C, 69.62; H, 5.58; N, 4.30%. $C_{19}H_{18}ClNO_2$ requires: C, 69.62; H, 5.53; N, 4.27%.

5-Benzyloxy-1-(3-iodopropyl)indole-3-carboxaldehyde

This was prepared from 5-benzyloxy-1-(3-iodopropyl)indole-3-carboxaldehyde according to the method described in Example 1 to give the product as an oil which was used immediately without further purification.

7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 5-benzyloxy-1-(3-chloropropyl)indole-3-carboxaldehyde according to the method described in Example 1 to give 1.55 g (40%) of the product as an off-white solid: mp 165-166 °C; IR ν_{max} (nujol)/cm^{-1}; 2925, 1640, 1458, 1228, 1136, 1033 and 723; NMR δ_H (400 MHz, $CDCl_3$) 2.68-2.72 (2H, m), 3.27 (2H, t, *J* 7.5 Hz), 4.10 (2H, t, *J* 7.6 Hz), 5.12 (2H, s), 6.92 (1H, d, *J* 2.6 Hz), 6.95-7.48 (6H, m), 7.82 (1H, s) and 9.89 (1H, s); Found: C, 78.02; H, 5.92; N, 4.70%. $C_{19}H_{17}NO_2$ requires: C, 78.33; H, 5.88; N, 4.81%.

1-(7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

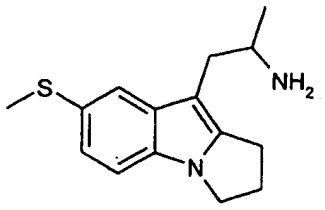
1-(7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 7-benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 to give 0.71 g (74%) of the product as a dark brown solid: mp 146-147 °C (decomp); IR ν_{max} (Nujol)/cm^{-1} 2925, 1626, 1465, 1267, 1208 and 855; NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 2.67-2.70 (2H, m), 3.09 (2H, t, *J* 7.1 Hz), 4.12 (2H, t, *J* 7.1 Hz), 5.11 (2H, s), 6.95 (1H, dd, *J* 8.7, 2.5 Hz), 7.13-7.47 (7H, m) and 8.35 (1H, s); Found: C, 72.17; H, 5.77; N, 7.95%. $C_{21}H_{20}N_2O_3$ requires: C, 72.40; H, 5.79; N, 8.04%.

(*RS*)-1-(7-Benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

This was prepared from 1-(7-benzyloxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.17g (18%) of the title compound as an off-white solid: mp darkens at 180 °C, melts over 188-198 °C; IR ν_{max} (Nujol)/cm^{-1} 2923, 1626, 1464, 1222, 736 and 650; NMR δ_H (400 MHz, DMSO-d_6) 1.13 (3H, d, *J* 6.6 Hz), 2.50-2.56 (2H, m), 2.68-2.74 (1H, m), 2.87-2.96 (3H, m), 3.33-3.39 (1H, m), 3.99 (2H, t, *J* 7.5 Hz), 5.09 (2H, s), 6.43 (2H, s), 6.74-6.77 (1H,

dd, *J* 8.6, 2.5 Hz) and 7.15-7.48 (7H, m); Found: C, 67.84; H, 6.37; N, 6.30%. $C_{21}H_{24}N_2O.C_4H_4O_4.0.5H_2O$ requires: C, 67.40; H, 6.56; N, 6.29%.

Example 11: (*RS*)-1-(7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate



5-Methylthioindole-3-carboxaldehyde

5-Methylthioindole-3-carboxaldehyde was prepared from 5-methylthioindole (*Heterocycles*, **1992**, 34, 1169-1175) according to the method described in Example 1 to give 1.85 g (86%) of the product as a white solid: mp 182-183 °C; IR ν_{max} (Nujol)/cm^{-1} 3172, 2926, 2807, 1632, 1440, 1130 and 972; NMR δ_H (400 MHz, DMSO-d_6) 2.50 (3H, s), 7.24 (1H, dd, *J* 11.4, 2.8 Hz), 7.50 (1H, d, *J*, 11.5 Hz), 7.96 (1H, s), 8.28 (1H, s) and 9.92 (1H, s).

1-(3-Chloropropyl)-5-methylthio-indole-3-carboxaldehyde

1-(3-Chloropropyl)-5-methylthio-indole-3-carboxaldehyde was prepared from 5-methylthioindole-3-carboxaldehyde according to the method described in Example 1 to give 2.36 g (94%) of the product as a pale-yellow solid: mp 64-65 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 2809, 1656, 1534, 1399, 1172, 1027, 813 and 786; NMR δ_H (400 MHz, $CDCl_3$) 2.27-2.33 (2H, m), 2.54 (3H, s), 3.46 (2H, t, *J* 5.7 Hz), 4.38 (2H, t, *J* 6.5 Hz), 7.29 (2H, s), 7.71 (1H, s), 8.22 (1H, s) and 9.96 (1H, s).

1-(3-Iodopropyl)-5-methylthio-indole-3-carboxaldehyde

1-(3-Iodopropyl)-5-methylthio-indole-3-carboxaldehyde was prepared from 1-(3-chloropropyl)-5-methylthio-indole-3-carboxaldehyde according to the method described

in Example 1 to give the product as a pale-brown oil which was used immediately without further purification.

7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde

7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde was prepared from 1-(3-iodopropyl)-5-methylthio-indole-3-carboxaldehyde according to the method described in Example 1 to give 0.80 g (40%) of the product as a pale-yellow solid: mp 140-141 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 2724, 1639, 1465, 1029 and 820; NMR δ_H (400 MHz, $CDCl_3$) 2.53 (3H, s), 2.68-2.76 (2H, m), 3.28 (2H, t, *J* 7.5), 4.12 (2H, t, *J* 7.1 Hz), 7.14-7.22 (2H, m), 8.12 (1H, s) and 9.90 (1H, s).

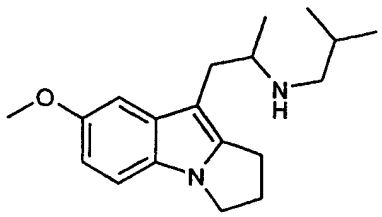
1-(7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene

1-(7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene was prepared from 7-methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde according to the method described in Example 1 to give 0.60 g (80%) of the product as an orange solid: mp 135-136 °C; IR ν_{max} (Nujol)/cm^{-1} 2924, 1636, 1475, 1277, 979 and 800; NMR δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s), 2.52 (3H, s), 2.66-2.70 (2H, m), 3.10 (2H, t, *J* 7.2 Hz), 4.14 (2H, t, *J* 7.1 Hz), 7.17-7.23 (2H, m), 7.54 (1H, s) and 8.35 (1H, s).

(*RS*)-1-(7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate

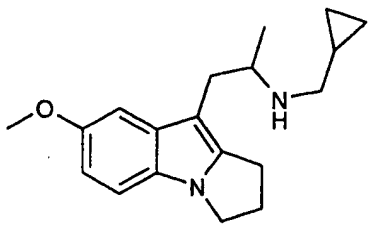
(*RS*)-1-(7-Methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine fumarate was prepared from 1-(7-methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-nitro-1-propene according to the method described in Example 3 to give 0.23 g (30%) of the title compound as pale-yellow crystals: mp 204-206 °C (dec.); IR ν_{max} (Nujol)/cm^{-1} 3052, 2924, 1612, 1463, 1310, 992 and 788; NMR δ_H (400 MHz, DMSO-d_6) 1.14 (3H, d, *J* 6.1 Hz), 2.46 (3H, s), 2.50-2.55 (2H, m), 2.71-2.76 (1H, m), 2.89-2.99 (3H, m), 3.34-3.36 (1H, m), 4.02 (2H, t, *J* 7.1Hz), 6.43 (2H, s), 7.04 (1H, dd, *J* 8.4, 1.9 Hz), 7.24 (1H, d, *J*, 8.1 Hz) and 7.50 (1H, d, *J* 1.4 Hz).

Example 12: (*RS*) *N*-(2-Methylpropyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride



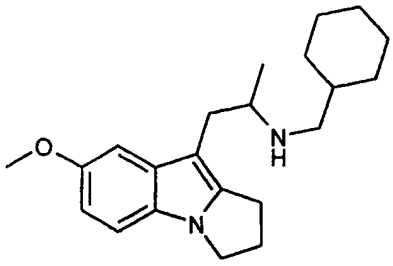
A mixture of (*RS*)-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine (0.030 g, 0.12 mmol), 3-methylpropanal (0.021 mL, 0.24 mmol) and methanol (1 mL) was shaken for 3 h. To the mixture was added Amberlite IRA-400 borohydride resin (2.5 mmol/g $-BH_4$, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h. To the mixture was added PS-benzaldehyde (2.5 mmol/g –CHO, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL) and the filtrate was concentrated *in vacuo*. The concentrate was dissolved in dichloromethane (2 mL) and Amberlyst-15 (0.5 g) was added. The mixture was shaken for 1 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL), suspended in methanolic ammonia solution (2 M, 1 mL, 2 mmol), shaken for 1 h, and filtered. The filter-cake was washed (dichloromethane) and the filtrate was concentrated *in vacuo*. The concentrate was treated with ethereal hydrogen chloride solution (1 M, 1 mL, 1 mmol) and concentrated *in vacuo* to give the product as a beige solid (0.02 g, 49%): mp 178-181 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.01 (6H, m) 1.17 (3H, d, *J* 6.5 Hz) 2.56 (2H, m) 2.77 (1H, m) 2.77 (1H, m) 2.86 (1H, m) 2.93 (2H, m) 3.22 (1H, m) 3.39 (1H, m) 3.51 (1H, m) 3.78 (3H, s) 4.02 (2H, t, *J* 7 Hz) 6.71 (1H, dd, *J* 2.5, 8.5 Hz) 7.11 (1H, s) 7.19 (1H, d, *J* 8.5 Hz).

Example 13: (*RS*) *N*-(Cyclopropylmethyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride



(*RS*) *N*-(Cyclopropylmethyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride was prepared from (*RS*)-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and cyclopropylcarboxaldehyde according to the method described in Example 12 to give 0.024 g (54%) of the product as a beige solid: mp 149-151 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.41 (2H, dd, *J* 5, 9 Hz) 0.62 (2H, d, *J* 9 Hz) 1.15 (3H, d, *J* 6.5 Hz) 2.56 (2H, m) 2.73 (1H, dd, *J* 10.5, 14 Hz) 2.93 (6H, m) 3.78 (3H, s) 4.02 (2H, t, *J* 7 Hz) 6.71 (1H, dd, *J* 2.5 9 Hz) 7.07 (1H, d, *J* 2.5 Hz) 7.19 (1H, d, *J* 9 Hz).

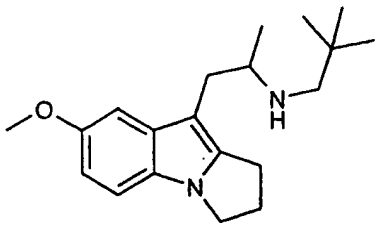
Example 14: (*RS*) *N*-(Cyclohexylmethyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride



(*RS*) *N*-(Cyclohexylmethyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride was prepared from (*RS*)-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and cyclohexylcarboxaldehyde according to the method described in Example 12 to give 0.023 g (50%) of the product as a beige solid: mp 210-3 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.01 (2H, m) 1.17 (3H, d, *J* 6.5 Hz) 1.22 (3H, m) 1.73 (6H, m) 2.55 (2H, m) 2.77 (1H, m) 2.84 (2H, m) 2.93 (2H, m)

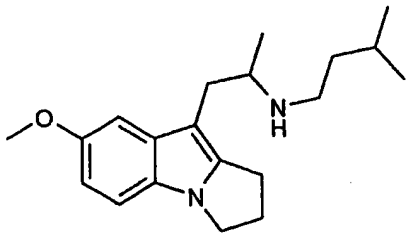
3.24 (1H, m) 3.39 (1H, m) 3.78 (3H, s) 4.02 (2H, t, *J* 7 Hz) 6.70 (1H, dd, *J* 2.5, 8.5 Hz) 7.13 (1H, d, *J* 2.5 Hz) 7.18 (1H, d, *J* 8.5 Hz).

Example 15: (*RS*) *N*-(2,2-Dimethylpropyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride



(*RS*) *N*-(2,2-Dimethylpropyl)-1-[(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride was prepared from from (*RS*)-(7-methoxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and 2,2-dimethylpropionaldehyde according to the method described in Example 12 to give 0.030 g (70%) of the product as a beige solid: mp 226-228 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.07 (9H, s) 1.17 (3H, d, *J* 6.5 Hz) 2.56 (2H, m) 2.65 (2H, m) 2.80 (1H, dd, *J* 11.5, 13.5 Hz) 2.89 (2H, t, *J* 6.5 Hz) 2.94 (1H, m) 3.25 (1H, m) 3.79 (3H, s) 4.02 (2H, t, *J* 7 Hz) 6.71 (1H, dd, *J* 2.5 8.5 Hz) 7.17 (1H, s) 7.20 (1H, d, *J* 8.5 Hz).

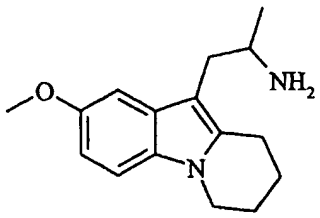
Example 16: (*RS*) *N*-(3-Methylbutyl)-1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride



(*RS*) *N*-(3-Methylbutyl)-1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)]-2-propylamine hydrochloride was prepared from from (*RS*)-(7-methoxy-2,3-dihydro-1*H*-

pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and 3-methylbutyraldehyde according to the method described in Example 12 to give 0.016 g (38%) of the product as a beige solid: mp 118-121 °C; NMR δ_H (400 MHz, DMSO-d_6) 0.92 (6H, d, *J* 14.5 Hz) 1.17 (3H, d, *J* 6.5 Hz) 1.55 (2H, m) 1.67 (2H, m) 2.55 (2H, m) 2.74 (1H, dd, *J* 10, 14 Hz) 2.94 (2H, m) 2.97 (2H, m) 3.19 (1H, dd, *J*, 4, 14 Hz) 3.78 (3H, s) 4.02 (2H, t, *J* 7 Hz) 6.71 (1H, dd, *J* 2.5, 8.5 Hz) 7.08 (1H, d, *J* 2.5 Hz) 7.19 (1H, d, *J* 8.5 Hz).

Example 17: (*RS*)-1-(2-Methoxy-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indol-10-yl)-2-propylamine fumarate



5-Methoxyindole-3-carboxaldehyde

To stirred dimethylformamide is added dropwise phosphorus oxychloride. The mixture is stirred for 10 min and a solution of 5-methoxyindole in dimethylformamide is added dropwise. The mixture is heated to 40 °C for 45 min, cooled to room temperature and then treated with a solution of sodium hydroxide in water. The mixture is heated to 50 °C for 10 min, cooled to room temperature, poured onto crushed ice and filtered. The filter cake is recrystallised (methanol) to give the product as a white solid.

5-Methoxy-1-(4-chlorobutyl)indole-3-carboxaldehyde

To a stirred mixture of powdered potassium hydroxide in methyl sulfoxide is added dropwise a solution of 5-methoxyindole-3-carboxaldehyde in methyl sulfoxide. The mixture is stirred for 30 min and 1-bromo-4-chlorobutane is added dropwise. The mixture is stirred for 1 h and partitioned between ethyl acetate and water. The combined organic extracts are washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

5-Methoxy-1-(4-iodobutyl)indole-3-carboxaldehyde

A stirred solution of 5-methoxy-1-(4-chlorobutyl)indole-3-carboxaldehyde and sodium iodide in acetonitrile under argon is heated under reflux for 18 h, cooled to room temperature and partitioned between ether and water. The combined organic extracts are washed (aqueous sodium metabisulfite solution, water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

2-Methoxy-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indole-10-carboxaldehyde

To a stirred solution of 5-methoxy-1-(4-iodobutyl)indole-3-carboxaldehyde in toluene at reflux under argon is added dropwise over 2 h a solution of 1,1'-azobis(cyclohexanecarbonitrile) and tri-n-butyltin hydride in toluene. The mixture is stirred for 3 h, cooled to room temperature, and potassium fluoride and water are added. The mixture is stirred for 18 h and filtered through a pad of kieselguhr. The filter-cake is washed (ethyl acetate) and the filtrate is concentrated *in vacuo* and purified by column chromatography to give the product.

1-(2-Methoxy-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indol-10-yl)-2-nitro-1-propene

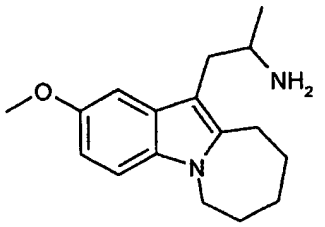
A stirred solution of 2-methoxy-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indole-10-carboxaldehyde and ammonium acetate in nitroethane is heated to 100 °C for 1 h, cooled to room temperature and partitioned between ethyl acetate and water. The combined organic extracts are washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

(*RS*)-1-(2-Methoxy-6,7,8,9-Tetrahydro-pyrido[1,2-*a*]indol-10-yl)-2-propylamine fumarate

To a stirred solution of lithium aluminium hydride in tetrahydrofuran under argon is added dropwise a solution of 1-(2-methoxy-6,7,8,9-tetrahydro-1*H*-pyrido[1,2-*a*]indol-10-yl)-2-nitro-1-propene in tetrahydrofuran. The mixture is heated under reflux for 4 h

and cooled to 0 °C. To the mixture is added dropwise aqueous potassium sodium tartrate solution and the mixture is stirred for 30 min and filtered through kieselguhr. The filtrate is extracted with dichloromethane. The combined organic extracts are washed (water, brine), dried (sodium sulfate), concentrated *in vacuo*, dissolved in hot 2-propanol and added dropwise to a stirred solution of fumaric acid in 2-propanol at 50 °C. The mixture is cooled to 0 °C and filtered. The filter-cake is washed (2-propanol, ether) and dried to give the product.

Example 18: (*RS*)-1-(2-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)-2-propylamine fumarate



5-Methoxyindole-3-carboxaldehyde

To stirred dimethylformamide is added dropwise phosphorus oxychloride. The mixture is stirred for 10 min and a solution of 5-methoxyindole in dimethylformamide is added dropwise. The mixture is heated to 40 °C for 45 min, cooled to room temperature and then treated with a solution of sodium hydroxide in water. The mixture is heated to 50 °C for 10 min, cooled to room temperature, poured onto crushed ice and filtered. The filter cake is recrystallised (methanol) to give the product as a white solid.

5-Methoxy-1-(5-chloropentyl)indole-3-carboxaldehyde

To a stirred mixture of powdered potassium hydroxide in methyl sulfoxide is added dropwise a solution of 5-methoxyindole-3-carboxaldehyde in methyl sulfoxide. The mixture is stirred for 30 min and 1-bromo-5-chloropentane is added dropwise. The mixture is stirred for 1 h and partitioned between ethyl acetate and water. The

combined organic extracts are washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

5-Methoxy-1-(5-iodopentyl)indole-3-carboxaldehyde

A stirred solution of 5-methoxy-1-(5-chloropentyl)indole-3-carboxaldehyde and sodium iodide in acetonitrile under argon is heated under reflux for 18 h, cooled to room temperature and partitioned between ether and water. The combined organic extracts are washed (aqueous sodium metabisulfite solution, water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

2-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carboxaldehyde

To a stirred solution of 5-methoxy-1-(5-iodopentyl)indole-3-carboxaldehyde in toluene at reflux under argon is added dropwise over 2 h a solution of 1,1'-azobis(cyclohexanecarbonitrile) and tri-n-butyltin hydride in toluene. The mixture is stirred for 3 h, cooled to room temperature, and potassium fluoride and water are added. The mixture is stirred for 18 h and filtered through a pad of kieselguhr. The filter-cake is washed (ethyl acetate) and the filtrate is concentrated *in vacuo* and purified by column chromatography to give the product.

1-(2-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)-2-nitro-1-propene

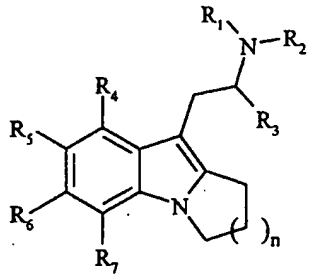
A stirred solution of 2-methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole-11-carboxaldehyde and ammonium acetate in nitroethane is heated to 100 °C for 1 h, cooled to room temperature and partitioned between ethyl acetate and water. The combined organic extracts are washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product.

(*RS*)-1-(2-Methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)-2-propylamine fumarate

To a stirred solution of lithium aluminium hydride in tetrahydrofuran under argon is added dropwise a solution of 1-(2-methoxy-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indol-11-yl)-2-nitro-1-propene in tetrahydrofuran. The mixture is heated under reflux for 4 h and cooled to 0 °C. To the mixture is added dropwise aqueous potassium sodium tartrate solution and the mixture is stirred for 30 min and filtered through kieselguhr. The filtrate is extracted with dichloromethane. The combined organic extracts are washed (water, brine), dried (sodium sulfate), concentrated *in vacuo*, dissolved in hot 2-propanol and added dropwise to a stirred solution of fumaric acid in 2-propanol at 50 °C. The mixture is cooled to 0 °C and filtered. The filter-cake is washed (2-propanol, ether) and dried to give the product.

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

n is 1, 2 or 3;

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, or R_5 and R_6 together form a carbocyclic or heterocyclic ring,

and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 wherein n=1.

3. A compound according to claim 1 or 2 wherein R_1 and R_2 are hydrogen.

4. A compound according to claim 1 or 2 wherein R_1 is hydrogen and R_2 is alkyl.

5. A compound according to claim 1 or 2 wherein R_1 is hydrogen and R_2 is arylalkyl.

6. A compound according to any preceding claim wherein R_3 is methyl.

7. A compound according to any preceding claim wherein R_4 to R_7 are selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl.

8. A compound according to any preceding claim wherein R_4 is hydrogen or halogen.

9. A claim according to any preceding claim wherein R_5 is other than hydrogen.

10. A compound according to any preceding claim wherein R_5 is selected from halogen, alkyl, alkoxy and alkylthio.

11. A compound according to any preceding claim wherein R_6 is other than hydrogen.

12. A compound according to any of claims 1 to 10 wherein R_6 is selected from hydrogen and halogen.

13. A compound according to any of claims 1 to 8 wherein R_5 and R_6 together form an O, S or N containing heterocyclic ring.

14. A compound according to claim 13 wherein said ring contains 5 or 6 heteroatoms.

15. A compound according to any one of claims 1 to 14 wherein R_7 is hydrogen.

16. A compound according to any preceding claim wherein two or three of R_4, R_5, R_6 and R_7 are hydrogen.

17. A compound according to claim 1 wherein the compounds of formula (I) are selected from 1-(7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(6,7-difluoro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(7-bromo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine, 1-(7-methoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine and 1-(7-methylthio-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-2-propylamine.

18. A compound according to any preceding claim which is the (*S*)-enantiomer thereof.

19. A compound of formula (I) as set out in any one of claims 1 to 18 for use in therapy.

20. The use of a compound of formula (I) as set out in any of claims 1 to 18 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

21 A use according to claim 20 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

22. A use according to claim 20 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

23. A use according to claim 22 wherein said toxic or infective CNS disease is encephalitis or meningitis.

24. A use according to claim 20 wherein the cardiovascular disorder is thrombosis.

25. A use according to claim 20 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

26. A use according to claim 20 wherein said medicament is for the treatment of obesity.

27. A method of treatment of any of the disorders set out in claims 20 to 26 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 8.

28. A use or method according to any of claims 20 to 27 wherein said treatment is prophylactic treatment.

29. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 18.

30. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 18 in combination with a pharmaceutically acceptable carrier or excipient.

31. A method of making a composition according to claim 30 comprising combining a compound of formula (I) as set out in any one of claims 1 to 18 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/02884

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D471/04 C07D491/14 A61K31/40
//(C07D487/04,209:00,209:00),(C07D487/04,223:00,209:00),
(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BÖS ET AL.: "Novel agonists of 5HT2c receptors..." J.MED.CHEM., vol. 40, 1997, pages 2762-2769, XP002124267 see compound 15 page 2763; table 1 --- -/--	1-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 1999	16/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/02884

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BOS M JENCK F MARTIN JR MOREAU JL MUTEL V SLEIGHT AJ WIDMER U: "Synthesis, pharmacology and therapeutic potential of 10-methoxypyrazino'1,2-a!indoles, partial agonists at the 5HT2C receptor" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA,FR,EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, vol. 32, no. 3, page 253-261 XP004075426 ISSN: 0223-5234 page 254; table 1 ---	1-31
A	WO 93 18036 A (SMITHKLINE BEECHAM PLC) 16 September 1993 (1993-09-16) claim 1 ---	1-31
A	CLARK ET AL.: "2-(Quinuclidin-3-yl)pyrido'4,3-b!indol-1-ones ..." J.MED.CHEM., vol. 36, no. 18, 1993, pages 2645-2657, XP002124268 see page 2646, table I, compounds 12,13 ---	1-31
A	EP 0 327 307 A (GLAXO GROUP LTD) 9 August 1989 (1989-08-09) claim 1 ---	1-31
A	US 3 250 783 A (REMERS) 10 May 1966 (1966-05-10) claim 1 ---	1-31
A	EP 0 167 901 A (SOBIO LAB) 15 January 1986 (1986-01-15) cited in the application claim 1 -----	1-31

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...nformation on patent family members

Interr ...nal Application No
PCT/GB 99/02884

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9318036 A	16-09-1993	AP 401 A	29-08-1995
		AT 180785 T	15-06-1999
		AU 671102 B	15-08-1996
		CA 2131797 A	16-09-1993
		CN 1078471 A,B	17-11-1993
		CZ 9402210 A	13-09-1995
		DE 69325167 D	08-07-1999
		EP 0630376 A	28-12-1994
		EP 0884319 A	16-12-1998
		ES 2132223 T	16-08-1999
		FI 944204 A	12-09-1994
		HU 71121 A	28-11-1995
		IL 105003 A	12-09-1996
		JP 2831467 B	02-12-1998
		JP 7504433 T	18-05-1995
		MX 9301348 A	01-09-1993
		NO 943348 A	09-11-1994
		NZ 249565 A	27-07-1997
		SG 50693 A	20-07-1998
		SI 9300114 A	31-12-1993
		SK 107894 A	12-04-1995
		US 5852014 A	22-12-1998
		ZA 9301709 A	18-01-1994
		AU 4081393 A	30-12-1993
		CN 1085083 A	13-04-1994
		EP 0641198 A	08-03-1995
		WO 9324117 A	09-12-1993
		JP 7507290 T	10-08-1995
		MX 9302985 A	01-11-1993
		US 5763459 A	09-06-1998
EP 0327307 A	09-08-1989	JP 1308277 A	12-12-1989
		US 4963546 A	16-10-1990
		US 5026696 A	25-06-1991
US 3250783 A	10-05-1966	NONE	
EP 0167901 A	15-01-1986	AT 51623 T	15-04-1990
		AU 583520 B	04-05-1989
		AU 4424385 A	02-01-1986
		CA 1296730 A	03-03-1992
		ES 544729 A	16-11-1986
		ES 552653 A	16-03-1987
		ES 552654 A	16-03-1987
		ES 552655 A	16-03-1987
		GR 851602 A	25-11-1985
		IE 58102 B	30-06-1993
		JP 1964274 C	25-08-1995
		JP 6099430 B	07-12-1994
		JP 61030587 A	12-02-1986
		MX 164198 B	23-07-1992
		NZ 212588 A	06-01-1989
		US 4853391 A	01-08-1989